UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
PO Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/988,842	11/19/2001	Jan Johansson	12125-002001	9389

26161 7590 06/02/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	13

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,842	JOHANSSON, JAN	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *3-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8 10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election **without** traverse of Group I (claims 1 and 2) in Paper No. 12 (5 March 2002) is acknowledged. Claims 3-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed 16 April 2002 (Paper No. 5) has been received and entered in full.

Drawings

3. The drawings are objected to because Figure 11 contains two parts, an "upper panel" and a "lower panel". These components should be labeled "11A" and "11B" in both the drawings and the specification. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims **1-2** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method of identifying a compound that stabilizes or can stabilize an α-helical conformation of a discordant helix in a polypeptide* <u>*in vitro*</u>, does not reasonably provide enablement for *practice of said method* <u>*in vivo*</u>. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

6. Claim 1 is drawn to a method of screening test compounds that stabilize an α-helical conformation of a discordant helix in a polypeptide comprising contacting a test polypeptide containing a discordant helix with a test compound and determining the rate of decrease of α-helices. Claim 1 is in essence, a method to determine the effect of the test compound on the discordant helices in a polypeptide over time. Claim 2 is drawn to a method of screening test compounds that can stabilize an α-helical conformation of a discordant helix in a polypeptide comprising contacting a test polypeptide containing a discordant helix with a test compound and determining the amount of α-helices remaining in a discordant helix containing polypeptide at an experimental endpoint. Claim 2 is in essence, a method to determine the final effect of a test compound on the discordant helices in a polypeptide.

7. The above invention is drawn to a screening method of said claims to identify compounds which affect discordant helix stability. The language of said claims encompasses both *in vivo* and

in vitro screening practice. The specification teaches a method of performing the claimed method in vitro with purified test polypeptides.

8. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to practice the disclosed method in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of screening method in *in vivo* based solely on its performance *in vitro* is highly problematic. Further, since the state of protein biochemistry is highly unpredictable, the disclosed *in vitro* method would not be considered enabling. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

9. The following references are cited herein to illustrate the state of the art of protein biochemistry.

10. On the nature of the invention, Lansbury (30 March 1999) "Evolution of amyloid: What normal protein folding may tell use about fibrillogenesis and disease." PNAS USA 96(7): 3342-3344 (**IDS # AGG**) teaches that conditions which influence proteins that are prone to aggregate or form fibrils, such as proteins which contain a discordant helix, can depend on factors which differ between *in vitro* environments and inside animals or patients (pp. 3342-3343). This is particularly important for "gain-of-function" mutations, which includes discordant helices, where the protein changes conformation due to intrinsic thermodynamics or the cellular environment

making correlation between *in vitro* and *in vivo* experiments difficult for the skilled artisan (pp. 3342 and 3344).

11. Concerning the breath of the claims, Dobson (23 July 1999) "Protein misfolding, evolution and disease." TIBS **24**(7): 329-332 (**IDS #AX**) teaches that *in vivo*, proteins are tightly controlled through a redundant system of compartmentalization, degradation processes, temperature, pH, and chaperones to discourage misfolding, aggregation, and fibrillization (pp. 331). As disclosed in the instant Specification, discordant helices thermodynamically drive proteins to form fibrils (pp. 2). Thus it is unlikely that *in vitro* and *in vivo* conditions can be reasonably encompassed by the invention without a level of unpredictability and undue experimentation necessary to remedy the inherent complications.

12. Therefore due to the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable test compound *in vivo*, the absence of working examples directed to known screening methods *in vivo*, the complex nature of the invention, the unpredictability of the effects of any given test compounds on experimental animal models and/or patients [Booth *et al.* (27 February 1997) "Instability, unfolding and aggregation of human lysozyme variants underlying amyloid fribrillogenesis." Nature **385**: 787-793 (**IDS #AT**)], and the breadth of the claims which fail to recite limitations for what constitutes an applicable experimental animal models to practice the claimed invention, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims **1** and **2** are rejected under 35 U.S.C. 102(b) as being anticipated by Soto *et al.* (24 September 1996) "Inhibition of Alzheimer's Amyloidosis by Peptides That Prevent β-Sheet Conformation." Biochemical and Biophysical Research Communications **226**(3): 672-680 (**IDS #ASS**).

14. Soto *et al.* teaches that pH, peptide concentration, and solvents can influence the conformation of Aβ peptides. These factors can determine whether the Aβ peptide adopts an α-helix or a β-sheet conformation. Soto *et al.* teaches that hydrophobicity facilitates monomeric interactions that thermodynamically drive Aβ peptides to convert from α-helices to β-sheets which produces amyloid fibrils (pp. 673). Soto *et al.* also teaches the use of a structure prediction algorithm to determine the probability that residues 15-25 of Aβ will form a β-sheet (Figure 1). While not specifically describing this as a "discordant helix" it meets all the limitations of "discordant helix" in the preamble of claims 1 and 2 as defined by the Specification (pp. 2 lines 15-17: "The invention relates to the discovery that a polypeptide containing an amino acid sequence that is predicted to be able to undergo a conversion from α-helix to β-strand can form fibrils. An amino acid sequence that is present as a helix in a polypeptide but is predicated to form a β-strand structure is herein termed a discordant helix.")

15. Soto *et al.* also teaches the use of iAβ1 to prevent the adoption of β-sheets in Aβ which favors the maintenance of α-helices (pp. 673, 678-679). Soto *et al.* teaches a method of determining the percentage of amyloid formed over time using iAβ1 including a control peptide,

a de facto screening method, thus meeting the limitations of claim 1 (Figure 2B, 3B, 4B-4F, and Table I).

16. Soto *et al.* also teaches the use of iAβ1 to prevent the adoption of β-sheets in Aβ which favors the maintenance of α-helices (pp. 673, 678-679). Soto *et al.* teaches a method of determining the percentage of amyloid formed per concentration of iAβ1 including a control peptide, a de facto screening method, thus meeting the limitations of claim 2 (Figure 2A, 3A, 4A, and Table I).

17. Claims **1** and **2** are rejected under 35 U.S.C. 102(b) as being anticipated by Salomon *et al.* (28 October 1996) "Nicotine Inhibits Amyloid Formation by the β-Peptide." Biochemistry **35**(42): 13568-13578 (**IDS #AOO**).

18. Salomon *et al.* clearly suggests performing a screening method to identify substances that prevent β-sheet formation in β-(1-42) peptide (also known as Aβ) (pp. 13568). It addition, Salomon *et al.* states:

> "The CD and NMR spectroscopic data suggest that the inhibition may result from the binding of nicotine to more soluble α-helical structure, which impedes an α-helix → β-sheet (soluble) → β-sheet (precipitate) process from occurring." (pp. 13568)

While not explicitly stating that nicotine does or can stabilize a discordant helix, Salomon *et al.* recites all the elements of the definition of a "discordant helix" as given in the instant Specification therefore rendering the concept in whole as disclosed prior to the filing of the instant application (pp. 2 lines 15-17). In addition, Salomon *et al.* proposes a model suggesting that α-helical stability as desirable to prevent the formation of amyloid and hence amyloidosis like Alzheimer's disease (Figure 7 and pp. 13577). Finally, Salomon et al. states:

> "The present study establishes that nicotine binds to the α-helical structure within residues 1-28 of the β-peptide which provides a rationale for the nicotine inhibition to β-sheet production and precipitation." (pp. 13576)

Thus Salomon *et al.* meets the limitations of the preamble of claims 1 and 2.

19. Salomon *et al.* teaches that the β-(1-42) peptide was pretreated with triflouroacetic acid to ensure the β-(1-42) peptide was in a coiled conformation before being contacting the test compounds, namely nicotine, cotinine, pyridine, and *N*-methylpyrrolidine (Materials and Methods pp. 13569 and Figure 1). Salomon *et al.* also teaches a method of measuring the percentage change from a helical conformation to a dominant β-sheet conformation using circular dichrosim (CD), ultraviolet spectroscopy, and nuclear magnetic resonance spectroscopy (Materials and Methods pp. 13569-13570).

20. Salomon *et al.* teaches a method of determining the rate of β-sheet formation (from a helical conformation) and subsequent amyloid formation measured in the presence and absence of nicotine, a de facto screening method, thus meeting the limitations of claim 1 (Figure 3A).

21. Salomon *et al.* teaches a method of determining the percentage of β-sheet formation (from a helical conformation) and subsequent amyloid formation measured in the presence and absence of nicotine, cotinine, pyridine, and *N*-methylpyrrolidine, a de facto screening method, thus meeting the limitations of claim 2 (Figure 3B).

Summary

22. Claims **1** and **2** are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
May 19, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER